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A Review on Local Asymptotic Stability Analysis for Mathematical Models of Hematopoiesis with Delay and Delay-Dependent Coefficients

(Local Asymptotic Stability Analysis for Delay Models)

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Abstract. Stability analysis of mathematical models of hematopoiesis (blood cell production process), described by differential equations with delay, needs to locate eigenvalues of characteristic equations that are usually exponential polynomial functions with delay-dependent coefficients. It is then more complicated than for ordinary differential equations to determine conditions for all roots to have negative real parts. We present, on three models of increasing complexity, the tools and method that can be used, with their advantages and their limitations. The method consists in the reduction of the problem to the localization of roots of a real function, these roots giving critical values of the delay for which stability possibly switches.

1 Introduction

Mathematical modeling of hematopoiesis, the process of production and regulation of blood cells, has attracted a lot of attention since the end of the 1970's and the pioneering work of Mackey [23]. Based on Lajtha [22] and Burns and Tannock [11] works, Mackey proposed a system of two ordinary differential equations with delay to describe the dynamics of hematopoietic stem cell (HSC) populations, and applied his model to a blood disease, aplastic anemia. Mackey's model has been later studied, and improved by many authors, including Mackey and co-workers [12, 13, 18], see also Adimy et al [2, 3, 4, 5, 6, 7, 8], and the references therein. Such models are relevant due to their ability to describe some hematological diseases [18], like leukemia, through instabilities and oscillatory behaviors.

Analysis of Mackey's models, and subsequent related models based on delay differential systems, lies on the ability to determine conditions for the

stability or the instability of steady states, and to characterize the change of stability. Global stability of steady states can sometimes be obtained with a Lyapunov function [5, 14, 15, 19], however for hematopoiesis models such conclusions can usually be reached only for the steady state describing cell extinction, which is consequently not the steady state expected to be asymptotically stable. For positive steady states, global stability is most of the time hard to establish, so determining local asymptotic stability represents a challenging work with potentially relevant results.

Local asymptotic stability of the steady state of a delay differential equation or system is obtained by studying a characteristic equation which is an exponential polynomial, and by locating eigenvalues with negative real parts. Loss of stability is obtained when eigenvalues cross on the imaginary axis [21]. Nevertheless, contrary to what happens with ordinary differential systems, the number of roots of an exponential polynomial is not finite, and determining explicitly its roots is usually impossible. In the case of hematopoiesis models, one difficulty is added: coefficients of the characteristic equations usually depend on the delay, either explicitly or implicitly through values of the steady states. Hence, analysis of the characteristic equations is often hard to perform.

We present here a review of some models of hematopoiesis dynamics for which exponential polynomial characteristic equations with delay-dependent coefficients must be studied in order to determine asymptotic stability of the positive steady state. Three different cases are presented with increasing degree of the polynomial part of the characteristic equation, and difficulties are stressed out. A new model of erythropoiesis (red blood cell production), based on Adimy et al. [4] and Crauste et al. [17], is proposed to illustrate the case of a 3rd degree exponential polynomial characteristic equation. Analysis is allowed due to a method developed by Beretta and Kuang [9] for delay-dependent coefficient characteristic equations. We present the pros and cons of this method in the framework of hematopoiesis modeling.

2 Models of Quiescent and Proliferating cells

In 1978, Mackey [23] proposed a model of hematopoietic stem cell dynamics, based on two distinct populations: a quiescent one and a proliferating one. Both cell populations can die, with different death rates, and the main assumptions are the following: (a) quiescent cells are randomly introduced in the proliferating phase with a rate depending on their own amount, and (b) proliferating cells age and divide a fixed time τ after their introduction

in the phase, to give two cells which immediately enter the quiescent phase. The model is illustrated in Figure 1.

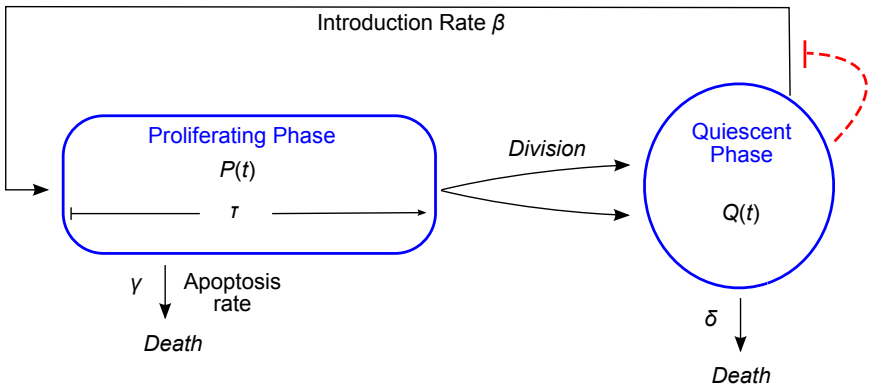

Figure 1: Schematic representation of HSC dynamics, from Mackey [23]. The dashed line represents the feedback control from quiescent cells on their own introduction in the proliferating phase.

The model has the form of a system of two differential equations with a discrete delay τ,

$$\frac{dQ}{dt}(t) = -\delta Q(t) - \beta(Q(t))Q(t) + 2e^{-\gamma\tau}\beta(Q(t-\tau))Q(t-\tau), \quad (2.1)$$

$$\frac{dP}{dt}(t) = -\gamma P(t) + \beta(Q(t))Q(t) - e^{-\gamma\tau}\beta(Q(t-\tau))Q(t-\tau), \quad (2.2)$$

where $Q(t)$ denotes the number of quiescent cells at time t, $P(t)$ the number of proliferating cells at time t, δ and γ the death rates, τ the length of the proliferating phase, and β is the introduction rate of quiescent cells into the proliferating phase. The rate β is assumed to depend on the number of quiescent cells $Q(t)$. The function β is naturally assumed to be decreasing, bounded and positive with $\lim_{Q\to\infty}\beta(Q) = 0$ [23].

Existence and uniqueness of solutions of system (2.1)–(2.2) can be deduced from Hale and Verduyn Lunel [19], by assuming the nonlinear term $\beta(Q)Q$ is a Lipschitz function. The same reasoning can be applied to examples considered in other Sections. Boundedness of solutions can also be rather easily obtained when death rates are supposed to be positive [5, 14, 15].

It is straightforward that equation (2.2) is decoupled from equation (2.1), so the analysis of (2.1)–(2.2) reduces to the analysis of equation (2.1). A

steady state of (2.1) is a solution $\overline{Q}$ satisfying

$$\frac{d\overline{Q}}{dt}(t) = 0 = (2e^{-\gamma\tau} - 1)\beta(\overline{Q})\overline{Q} - \delta\overline{Q}.$$

Hence, it is clear that (2.1) has one trivial steady state, $\overline{Q} = 0$, and a positive steady state $\overline{Q} = Q^*$, defined by

$$Q^* = \beta^{-1}\left(\frac{\delta}{2e^{-\gamma\tau} - 1},\right), \tag{2.3}$$

provided that

$$(2e^{-\gamma\tau} - 1)\beta(0) > \delta. \tag{2.4}$$

Inequality (2.4) describes a situation in which the maximum renewal rate $(2e^{-\gamma\tau}\beta(0))$ is larger than the disappearance rate $(\delta + \beta(0))$. Biologically, this condition is necessary for the survival of the cell population.

Global asymptotic stability of the trivial steady state may be obtained through a Lyapunov function [14, 19]. However, we are interested here in the stability of the positive steady state, and particularly in its local asymptotic stability, so we will not detail this point.

The characteristic equation of the linearized equation of (2.1) is

$$\Delta(\lambda, \tau) := \lambda + \delta + \beta^* - 2\beta^* e^{-\gamma\tau} e^{-\lambda\tau} = 0, \tag{2.5}$$

where $\beta^* = \beta(Q^*) + Q^*\beta'(Q^*)$. Contrary to an ordinary differential equation, the characteristic equation Δ defined in (2.5) is not a polynomial function but an exponential polynomial, of degree 1. Consequently, the characteristic equation has an infinite number of eigenvalues. Moreover, coefficients of the characteristic equation depend, explicitly or implicitly, on the delay τ (for instance, through the steady state value in β^*), and consequently locate the roots of Δ is not an easy task.

In order to analyze the stability of the positive steady state Q^* with respect to values of the parameters, in particular of the value of the delay τ, it is necessary to determine conditions for which stability can be ensured. To that aim, let's check whether the characteristic equation has roots with negative real parts when the delay τ equals zero. One gets

$$\Delta(\lambda, 0) := \lambda + \delta - \beta^*,$$

so there is only one real root in this case, $\lambda = \beta^* - \delta$, that is with (2.3), $\lambda = Q^*\beta'(Q^*) < 0$. Hence, the steady state is locally asymptotically stable in the absence of delay.

Beretta and Kuang [9] proposed a method to determine critical values of τ for which eigenvalues cross the imaginary axis, and so stability is lost. We illustrate this method on the above example, and we determine conditions for local asymptotic stability of the positive steady state Q^*.

Consider a characteristic function in the form of an exponential polynomial function

$$\Delta(\lambda,\tau) = R_1(\lambda,\tau) + R_2(\lambda,\tau)e^{-\lambda\tau}, \tag{2.6}$$

where R_1 and R_2 are two polynomial functions of λ with coefficients depending on the delay τ, satisfying $\deg(R_1(\lambda,.)) > \deg(R_2(\lambda,.))$. The following properties must be verified,

(i) $R_1(0,\tau) + R_2(0,\tau) \neq 0$;

(ii) $R_1(i\omega,\tau) + R_2(i\omega,\tau) \neq 0$;

(iii) $\limsup\left\{\left|\frac{R_2(\lambda,\tau)}{R_1(\lambda,\tau)}\right|; |\lambda| \to \infty, \mathrm{Re}\lambda \geq 0\right\} < 1$;

(iv) $F(\omega,\tau) := |R_1(i\omega,\tau)|^2 - |R_2(i\omega,\tau)|^2$ has a finite number of zeros,

in order to define a well-posed framework in which determining conditions on the parameters for the loss of stability (pure imaginary roots appear) is equivalent to locating a finite number of roots of an explicit function of the delay τ. For instance, condition **(i)** ensures that $\lambda = 0$ is not a root of Δ. Conditions **(i)** to **(iv)** must be verified for all $\tau \in [0, \tau_{\max})$ where $\tau_{\max}$ is, for instance, given by (2.4) (definition domain of the steady state).

Let us check that properties **(i)** to **(iv)** are satisfied on our example. First, one has, from (2.4),

$$R_1(0,\tau) + R_2(0,\tau) = \delta + \beta^* - 2\beta^* e^{-\gamma\tau} = -(2e^{-\gamma\tau} - 1)Q^*\beta'(Q^*) > 0. \tag{2.7}$$

Second,

$$R_1(i\omega,\tau) + R_2(i\omega,\tau) = -(2e^{-\gamma\tau} - 1)Q^*\beta'(Q^*) + i\omega \neq 0.$$

Third,

$$\limsup\left\{\left|\frac{R_2(\lambda,\tau)}{R_1(\lambda,\tau)}\right|; |\lambda| \to \infty, \mathrm{Re}\lambda \geq 0\right\} = 0 < 1.$$

Fourth,

$$F(\omega,\tau) := \omega^2 + (\delta + \beta^*)^2 - (2\beta^* e^{-\gamma\tau})^2.$$

It follows that $F(\omega,\tau)$ has a finite number of zeros,

$$\omega = \pm\left[(2\beta^* e^{-\gamma\tau})^2 - (\delta + \beta^*)^2\right]^{1/2}, \tag{2.8}$$

provided that

$$(2\beta^* e^{-\gamma\tau})^2 > (\delta + \beta^*)^2. \tag{2.9}$$

Thanks to (2.7), (2.9) is equivalent to

$$(2e^{-\gamma\tau} + 1)\beta^* + \delta < 0.$$

Condition (2.9) allows actually to define an interval $[0, \tau^*)$ in which one can search for critical values of τ. Hence, positive roots ω defined in (2.8) are in fact functions of the delay τ, so $\omega = \omega(\tau)$.

The method proposed by Beretta and Kuang [9] consists in determining critical values of τ using roots of $F(\cdot, \tau)$. Separating real and imaginary parts in (2.5) and searching for purely imaginary roots $\lambda = i\omega$ reduces to

$$\cos(\tau\omega(\tau)) = \frac{\delta + \beta^*}{2\beta^* e^{-\gamma\tau}}, \qquad \sin(\tau\omega(\tau)) = -\frac{\omega(\tau)}{2\beta^* e^{-\gamma\tau}}. \tag{2.10}$$

The problem now becomes to be able to find out values of τ satisfying (2.10). Indeed, by adding the squares of both equations in (2.10), one can check that values of ω and τ such that (2.10) is satisfied must verify $F(\omega, \tau) = 0$. Setting, for $\tau \in [0, \tau^*)$,

$$\tau_k(\tau) = \frac{1}{\omega(\tau)} \left[\arccos\left(\frac{\delta + \beta^*}{2\beta^* e^{-\gamma\tau}} \right) + 2k\pi \right], \qquad k \in \mathbb{N}_0,$$

where $\omega(\tau)$ is given by (2.8), values of τ for which $(\omega(\tau), \tau)$ given by (2.8) and (2.9) is a solution of (2.10) are roots of the functions

$$Z_k(\tau) := \tau - \tau_k(\tau), \qquad k \in \mathbb{N}_0, \tau \in [0, \tau^*). \tag{2.11}$$

Hence the problem of finding critical values of τ reduces to finding roots of a real function. The roots of Z_k can be found using popular software, yet they are hard to determine with analytical tools [9]. The following lemma states some properties of the Z_k functions [14], that are quite general in the kind of problems we focus on. We refer to [14] for the proof.

Lemma 2.1 *For $k \in \mathbb{N}_0$,*

$$Z_k(0) < 0 \qquad \textit{and} \qquad \lim_{\tau \to \tau^*} Z_k(\tau) = -\infty.$$

Therefore, provided that no root of Z_k is a local extremum, the number of positive roots of Z_k, $k \in \mathbb{N}_0$, on the interval $[0, \tau^*)$ is even. Moreover, if Z_k has no root on the interval $[0, \tau^*)$, then Z_j, with $j > k$, does not have positive roots.

The last statement in Lemma 2.1 implies, in particular, that, if Z_0 has no positive root, then (2.10) has no positive solution, and equation (2.5) does not have pure imaginary roots, so the steady state is always stable.

The analysis of functions $Z_k(\tau)$ allows determining values of the delay for which stability switches. An illustration is displayed in Figure 2, where functions Z_0, Z_1 and Z_2 have been drawn using Matlab, all defined by (2.11) with parameters from Crauste [14, 15]. One can observe that Z_0 has two positive roots, hence there are two critical values of the delay τ for which stability switches, whereas Z_1, and consequently Z_2, has no positive root. In order to determine the nature of the instability (Hopf bifurcation, etc.) related to critical values of the delay, it is however necessary to go deeper in the analysis. We do not want to focus on this point here, so we refer to [14, 21] for interested reader. We can however mention that it is possible to show that stability of Q^* switches through a Hopf bifurcation.

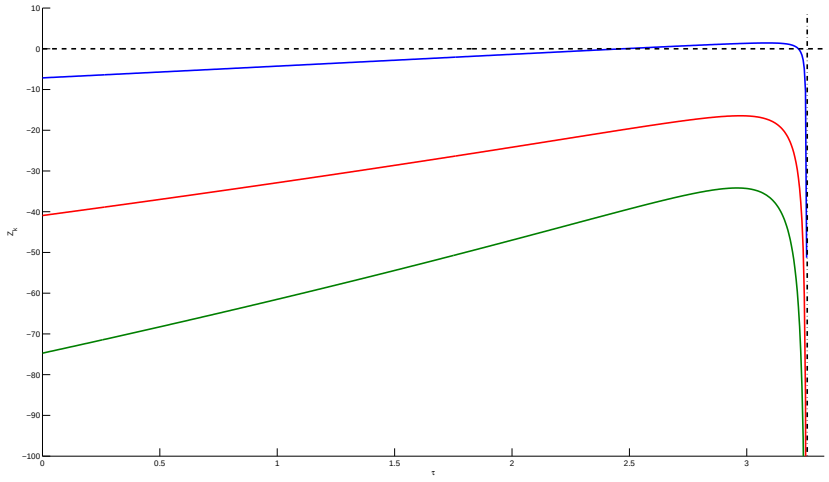

Figure 2: Functions Z_k, with $k = 1, 2, 3$, defined by (2.11). The above curve is Z_0, the middle one Z_1 and the bottom one Z_2. The vertical dashed curve on the right hand side indicates the value of τ^*.

A modification of Mackey's model, proposed in 2006 [14], considering an introduction rate depending on the total population of hematopoietic stem cells, $S(t) := P(t) + Q(t)$, also reduces to the study of a characteristic equation in the form of (2.5), when assuming death rates of both quiescent

and proliferating populations are the same. Considering different mortality rates leads to the following system [15],

$$\left\{\begin{array}{rcl} \dfrac{dQ}{dt}(t) & = & -[\delta+\beta(S(t))]Q(t)+2e^{-\gamma\tau}\beta(S(t-\tau))Q(t-\tau), \\ \dfrac{dS}{dt}(t) & = & -\gamma S(t)+(\gamma-\delta)Q(t)+e^{-\gamma\tau}\beta(S(t-\tau))Q(t-\tau). \end{array}\right.$$

This system also exhibits a positive steady state $(\overline{Q},\overline{S})=(Q^*,S^*)$, with $Q^*<S^*$. Its local asymptotic stability depends on the sign of eigenvalues of the characteristic equation (2.6), where

$$R_1(\lambda,\tau)=\lambda^2+[\delta+\gamma+\beta(S^*)]\lambda+\gamma(\delta+\beta(S^*))+Q^*\beta'(S^*)(\gamma-\delta)$$

and

$$R_2(\lambda,\tau)=-[Q^*\beta'(S^*)+2\beta(S^*)]e^{-\gamma\tau}\lambda+[Q^*\beta'(S^*)(\delta-2\gamma)-2\gamma\beta(S^*)]e^{-\gamma\tau}.$$

The characteristic equation is now a second degree exponential polynomial. We focus on such characteristic equations in the next section.

3 Models with 2 compartments

The method proposed by Beretta and Kuang [9], presented in the previous section, can be used to determine the appearance of pure imaginary roots for a priori any exponential polynomial characteristic equation, whatever the degree of the polynomial function. We focus here on a second degree exponential polynomial characteristic equation, arising for the local asymptotic stability analysis of the positive steady state of a model of hematopoiesis incorporating both dynamics of hematopoietic stem cells (see previous section) and a population of mature cells (either red blood cells, white cells or platelets) [4], see Figure 3. In this case, properties **(i)** to **(iii)** are usually straightforwardly satisfied.

As in the previous section consider two populations of hematopoietic stem cells, a quiescent one, whose density is denoted by $Q(t)$, and a proliferating one, whose density is $P(t)$. In addition, consider a population of mature cells $M(t)$ which controls, through a negative feedback, the introduction of quiescent cells in the proliferating phase, so, according to the notations defined in the previous section, $\beta=\beta(M(t))$. Denoting by K_Q (resp. K_P) the differentiation rate of quiescent (resp. proliferating) HSC

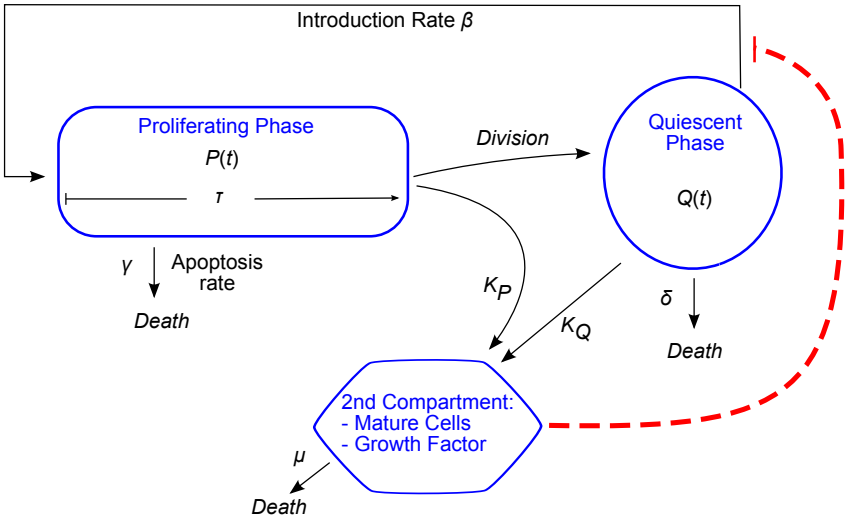

Figure 3: Schematic representation of a model of HSC dynamics with 2 compartments, from Adimy et al. [4], and one negative feedback control (dashed line).

into mature cells, the system we consider is then

$$\begin{cases} \dfrac{dP}{dt}(t) &= -\gamma P(t) + \beta(M(t))Q(t) - e^{-\gamma\tau}\beta(M(t-\tau))Q(t-\tau), \\ \dfrac{dQ}{dt}(t) &= -\left[\delta + K_Q + \beta(M(t))\right]Q(t) \\ &\quad +2(1-K_P)e^{-\gamma\tau}\beta\left(M(t-\tau)\right)Q(t-\tau), \\ \dfrac{dM}{dt}(t) &= -\mu M(t) + K_Q Q(t) + 2K_P e^{-\gamma\tau}\beta\left(M(t-\tau)\right)Q(t-\tau). \end{cases} \tag{3.1}$$

Under the assumption

$$\left[2(1-K_P)e^{-\gamma\tau} - 1\right]\beta(0) > \delta + K_Q,$$

system (3.1) has a positive steady state (P^*, Q^*, M^*), whose local asymptotic stability depends on the characteristic equation

$$\Delta(\lambda,\tau) := \lambda^2 + a_1(\tau)\lambda + a_2(\tau) + [a_3(\tau)\lambda + a_4(\tau)]e^{-\lambda\tau} = 0, \tag{3.2}$$

with

$$\begin{cases} a_1(\tau) &= \mu + \delta + K_Q + \beta(M^*), \\ a_2(\tau) &= \mu(\delta + K_Q + \beta(M^*)) + K_Q Q^*\beta'(M^*), \\ a_3(\tau) &= -2e^{-\gamma\tau}[K_P Q^*\beta'(M^*) + (1-K_P)\beta(M^*)], \\ a_4(\tau) &= -2e^{-\gamma\tau}[(\delta K_P + K_Q)Q^*\beta'(M^*) + \mu(1-K_P)\beta(M^*)]. \end{cases} \tag{3.3}$$

We first check that

$$\Delta(\lambda, 0) = \lambda^2 + [a_1(0) + a_3(0)]\lambda + [a_2(0) + a_4(0)]$$

has only roots with negative real parts. To that aim, one can use the Routh-Hurwitz criterion. Necessary and sufficient conditions for roots to have negative real parts are then

$$a_1(0) + a_3(0) > 0 \quad \text{and} \quad a_2(0) + a_4(0) > 0.$$

This is obtained from(3.3) and the definition of the steady state,

$$a_1(0) + a_3(0) = \mu - 2K_P R^* \beta'(M^*) > 0,$$

and

$$a_2(0) + a_4(0) = -2(\delta K_P + K_Q)Q^* \beta'(M^*) > 0.$$

Second, we check Beretta and Kuang's properties **(i)** to **(iv)**. One has

$$P(0,\tau) + Q(0,\tau) = \left[-2K_P \delta e^{-\gamma\tau} - (2e^{-\gamma\tau} - 1)K_Q\right] Q^* \beta'(M^*) > 0.$$

Moreover,

$$R_1(i\omega, \tau) + R_2(i\omega, \tau) = -\omega^2 + a_2(\tau) + a_4(\tau) + i\omega\left[a_1(\tau) + a_3(\tau)\right] \neq 0.$$

Furthermore, it is straightforward that

$$\limsup\left\{\left|\frac{a_3(\tau)\lambda + a_4(\tau)}{\lambda^2 + a_1(\tau)\lambda + a_2(\tau)}\right|; |\lambda| \to \infty, Re(\lambda) \geq 0\right\} = 0 < 1.$$

Finally, let define the polynomial function

$$F(\omega, \tau) := |R_1(i\omega, \tau)|^2 - |R_2(i\omega, \tau)|^2,$$

that is

$$F(\omega, \tau) = \omega^4 + [a_1^2(\tau) - 2a_2(\tau) - a_3^2(\tau)]\omega^2 + a_2^2(\tau) - a_4^2(\tau).$$

It is clear that F has a finite number of roots. However, contrary to the example developed in the previous section, it is not so trivial to exhibit explicit roots of function F. Assuming

$$\begin{cases} a_2^2(\tau) - a_4^2(\tau) < 0, & \text{or} \\ \dfrac{[a_1^2(\tau) - 2a_2(\tau) - a_3^2(\tau)]^2}{4} \geq a_2^2(\tau) - a_4^2(\tau) \geq 0 > a_1^2(\tau) - 2a_2(\tau) - a_3^2(\tau), \end{cases}$$

then $F(\cdot,\tau)$ has at least one positive root, and so there exists at least one $\omega = \omega(\tau) > 0$ such that $F(\omega(\tau),\tau) = 0$. One can assume there exists $\tau^* > 0$ such that $F(\cdot,\tau)$ has positive roots for $\tau \in [0,\tau^*)$ [4].

Now, searching for pure imaginary roots of (3.2), $\lambda = i\omega$, where $\omega = \omega(\tau)$ is a positive root of $F(\cdot,\tau)$ and $\tau \in [0,\tau^*)$, then it is possible, by separating real and imaginary parts in $\Delta(i\omega,\tau) = 0$, to define $\theta(\tau) \in [0,2\pi]$, such that

$$\begin{aligned}\cos(\theta(\tau)) &= \frac{[a_4(\tau) - a_1(\tau)a_3(\tau)]\omega^2(\tau) - a_2(\tau)a_4(\tau)}{a_4^2(\tau) + a_3^2(\tau)\omega^2(\tau)},\\ \sin(\theta(\tau)) &= \frac{a_3(\tau)\omega^3(\tau) + [a_1(\tau)a_4(\tau) - a_2(\tau)a_3(\tau)]\omega}{a_4^2(\tau) + a_3^2(\tau)\omega^2(\tau)}.\end{aligned}$$

Then one can check that $i\omega(\tau)$ is a root of (3.2) if and only if

$$\tau\omega(\tau) = \theta(\tau) + 2k\pi, \quad k \in \mathbb{N}_0,$$

that is, if τ is a root of the function

$$Z_k(\tau) = \tau - \frac{1}{\omega(\tau)}[\theta(\tau) + 2k\pi], \quad \tau \in [0,\tau^*),\ k \in \mathbb{N}_0.$$

Stability of the positive steady state can then be deduced similarly to what has been presented in the previous section. It is however noticeable that obtaining conditions for the stability of the positive steady state has proved to be more difficult for a second degree exponential polynomial characteristic equation than for a first degree exponential polynomial characteristic equation. Indeed, the main difficulty lies in the ability to find conditions for the existence of positive roots (and potentially exact values of the positive roots) of a polynomial function, F, with the same degree (as a function of ω^2) than the characteristic equation. It becomes clear then that increasing the complexity of the model, for instance by including cell compartments, or external factors involved in hematopoiesis, will increase difficulties to establish local asymptotic stability analytically due to the difficulty to identify roots of polynomial functions of high degree.

Similar examples may arise from the study of a model accounting for the influence of both quiescent and proliferating cells on the proliferation rate [15], as mentioned in the end of the previous section, a model including growth factor influence [1], a delay differential system with two delays [7] or from a system with a continuous distributed delay [17].

In the next section we focus on the stability of a third degree exponential polynomial characteristic equation arising from the linearisation of a more complex model of hematopoiesis dynamics, considering different levels of cell maturity and feedback controls acting at different time scales.

4 Models with 3 compartments

Mathematical models of hematopoiesis dynamics leading to the study of a third degree exponential polynomial characteristic equation in order to determine the stability of a positive steady state have been developed to consider, in addition to a hematopoietic stem cell population made of quiescent and proliferating cells: both a growth factor concentration, acting on HSC fate, and a mature cell population controlling the release of growth factors [8]; the effect of a growth factor acting on a mortality rate [2]; the effect of two growth factors, with two different targets [3].

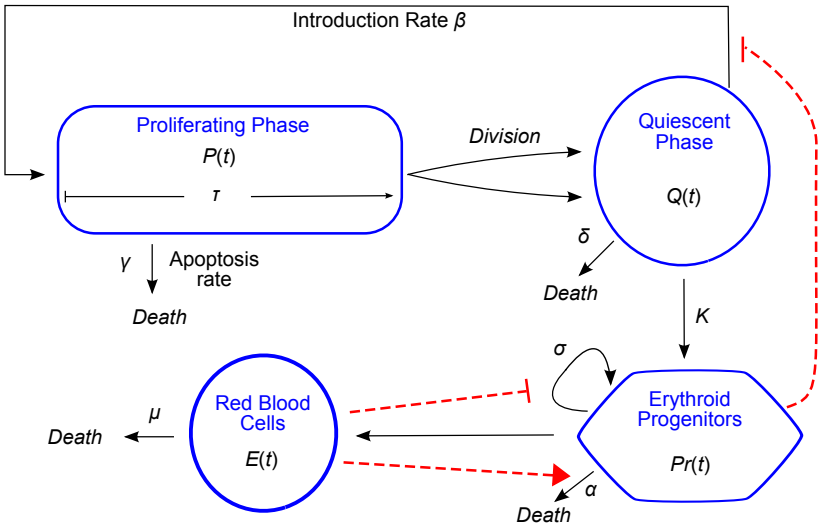

Figure 4: Schematic representation of a model of erythropoiesis including HSC dynamics, erythroid progenitor dynamics and red blood cell dynamics (3 compartments), as well as three short-term feedback controls, one positive and two negative (dashed lines).

We consider here a new model, inspired by Adimy et al [4] and Crauste et al. [17] (see Figure 4). It consists in the coupling of a HSC dynamics model and a model of erythropoiesis (red blood cell production). This latter model considers two populations of erythroid cells, immature cells called progenitors and mature cells called erythrocytes (or red blood cells), interacting with each other. Mature red blood cells exert a positive feedback on erythroid progenitor apoptosis (this feedback control is in fact mediated by erythropoietin, a growth factor known to inhibit erythroid progenitor apop-

tosis [20], which is not explicitly considered here) and a negative feedback on their proliferation [17]. Erythroid progenitors exert a negative feedback on HSC proliferation. Hence this model couples two short-term negative feedback controls in order to describe erythropoiesis.

Similarly to the previous section, denote by $Q(t)$ and $P(t)$ the quiescent and proliferating HSC amounts at time t, with death rates given respectively by δ and γ, and denote by β the introduction rate of quiescent cells in the proliferating phase. Moreover, denote by $Pr(t)$ the amount of erythroid progenitors at time t. These cells are produced by differentiation of quiescent HSC with a rate K, die by apoptosis with a rate α depending on the total number of circulating red blood cells, denoted by $E(t)$, and proliferate with a rate σ depending also on $E(t)$. Erythroid progenitors also negatively influence introduction of quiescent cells in the proliferating phase, so $\beta = \beta(Pr(t))$. Finally, red blood cells die with a constant rate μ, and are produced from erythroid progenitors with a rate ξ. An amplification coefficient A is also considered.

All functions $\beta(Pr)$, $\sigma(E)$ and $\alpha(E)$ are supposed to be continuously differentiable, bounded and positive. The introduction rate β is supposed to be a decreasing function of the variable $Pr(t)$, with $\lim_{Pr\to+\infty}\beta(Pr)=0$. Similarly, the proliferation rate σ is assumed to be a decreasing function of $E(t)$, with $\lim_{E\to+\infty}\sigma(E)=0$. The apoptosis rate, on the contrary, is supposed to be an increasing function of $E(t)$ with $\alpha(0)=0$ [17].

Variables $P(t)$, $Q(t)$, $Pr(t)$ and $E(t)$ satisfy the following system of delay differential equations,

$$\begin{cases} \dfrac{dP}{dt}(t) = -\gamma P(t) + \beta(Pr(t))Q(t) - e^{-\gamma\tau}\beta(Pr(t-\tau))Q(t-\tau), \\ \dfrac{dQ}{dt}(t) = -\left[\delta + K + \beta(Pr(t))\right]Q(t) + 2e^{-\gamma\tau}\beta\left(Pr(t-\tau)\right)Q(t-\tau), \\ \dfrac{dPr}{dt}(t) = [\sigma(E(t)) - \alpha(E(t)) - \xi]Pr(t) + KQ(t), \\ \dfrac{dE}{dt}(t) = -\mu E(t) + A\xi Pr(t). \end{cases} \tag{4.1}$$

Steady states of system (4.1) are solutions $(\overline{P}, \overline{Q}, \overline{Pr}, \overline{E})$ satisfying

$$\begin{cases} \left[(2e^{-\gamma\tau}-1)\beta(\overline{Pr}) - \delta - K\right]\overline{Q} = 0, \\ \left[\alpha(\overline{E}) + \xi - \sigma(\overline{E})\right]\overline{Pr} = K\overline{Q}, \end{cases} \tag{4.2}$$

and $\gamma\overline{P} = (1-e^{-\gamma\tau})\beta(\overline{Pr})\overline{Q}$ and $\mu\overline{E} = A\xi\overline{Pr}$.

One steady state, $(P_0, Q_0, Pr_0, E_0) = (0,0,0,0)$, always exists. It can be shown that this equilibrium is locally asymptotically stable when it is the only steady state. It describes extinction of all cell populations.

A second steady state is $(0, 0, Pr_1, E_1)$, where $\sigma(E_1) = \alpha(E_1) + \xi$ and $A\xi Pr_1 = \mu E_1$. This steady state exists provided that $\sigma(0) > \xi$ (see (4.2)). It corresponds to the extinction of HSCs and survival of more mature cells. This situation being biologically unrealistic, it is expected to be unstable.

Finally, the third steady state is (P_2, Q_2, Pr_2, E_2), where

$$(2e^{-\gamma\tau} - 1)\beta(Pr_2) = \delta + K,$$

and positive values of Q_2, P_2 and E_2 follow from (4.2). This steady state exists provided that

$$(2e^{-\gamma\tau} - 1)\beta(0) > \delta + K \tag{4.3}$$

and

$$\alpha\left(\frac{A\xi}{\mu}Pr_2\right) + \xi > \sigma\left(\frac{A\xi}{\mu}Pr_2\right). \tag{4.4}$$

Linearization of system (4.1) about one of its steady states leads to the following characteristic equation,

$$\lambda^3 + a_1(\tau)\lambda^2 + a_2(\tau)\lambda + a_3(\tau) + [a_4(\tau)\lambda^2 + a_5(\tau)\lambda + a_6(\tau)]e^{-\lambda\tau} = 0, \tag{4.5}$$

with

$$\begin{aligned}
a_1(\tau) &= \mu + \delta + K + \beta(\overline{Pr}) + \alpha(\overline{E}) + \xi - \sigma(\overline{E}),\\
a_2(\tau) &= \mu(\delta + K + \beta(\overline{Pr})) + (\delta + K + \beta(\overline{Pr}))(\alpha(\overline{E}) + \xi - \alpha(\overline{E}))\\
&\quad +\mu(\alpha(\overline{E}) + \xi - \alpha(\overline{E})) + K\overline{Q}\beta'(\overline{Pr}) + A\xi(\alpha'(\overline{E}) - \sigma'(\overline{E}))\overline{Pr},\\
a_3(\tau) &= \mu(\delta + K + \beta(\overline{Pr}))(\alpha(\overline{E}) + \xi - \sigma(\overline{E})) + \mu K\overline{Q}\beta'(\overline{Pr})\\
&\quad +A\xi(\alpha'(\overline{E}) - \sigma'(\overline{E}))\overline{Pr}(\delta + K + \beta(\overline{Pr})),\\
a_4(\tau) &= -2e^{-\gamma\tau}\beta(\overline{Pr}),\\
a_5(\tau) &= 2e^{-\gamma\tau}[-\mu\beta(\overline{Pr}) - \beta(\overline{Pr})(\alpha(\overline{E}) + \xi - \sigma(\overline{E})) - K\overline{Q}\beta'(\overline{Pr})],\\
a_6(\tau) &= 2e^{-\gamma\tau}[-\mu\beta(\overline{Pr})(\alpha(\overline{E}) + \xi - \sigma(\overline{E})) - \mu K\overline{Q}\beta'(\overline{Pr})\\
&\quad -A\xi(\alpha'(\overline{E}) - \sigma'(\overline{E}))\overline{Pr}\beta(\overline{Pr})].
\end{aligned}$$

Let focus on the local asymptotic stability of (P_2, Q_2, Pr_2, E_2). When $\tau = 0$, eigenvalues have negative real parts if and only if (Routh-Hurwitz criterion),

$$a_1(0) + a_4(0) > 0, \qquad a_3(0) + a_6(0) > 0$$

and

$$[a_1(0) + a_4(0)][a_2(0) + a_4(0)] > a_3(0) + a_6(0).$$

One gets, from(4.4),

$$\begin{aligned}
a_1(0) + a_4(0) &= \mu + \alpha(E_2) + \xi - \sigma(E_2) > 0,\\
a_3(0) + a_6(0) &= -\mu K Q_2 \beta'(Pr_2) > 0,
\end{aligned}$$

and

$$a_2(0)+a_5(0)=\mu(\alpha(E_2)+\xi-\sigma(E_2))+A\xi(\alpha'(E_2)-\sigma'(E_2))Pr_2-KQ_2\beta'(Pr_2)>0.$$

Moreover, since

$$\begin{aligned}&[\mu+\alpha(E_2)+\xi-\sigma(E_2)][\mu(\alpha(E_2)+\xi-\sigma(E_2))\\&+A\xi(\alpha'(E_2)-\sigma'(E_2))Pr_2]>Pr_2\beta'(Pr_2)[\alpha(E_2)+\xi-\sigma(E_2)]^2,\end{aligned}$$

then the steady state (P_2, Q_2, Pr_2, E_2) is locally asymptotically stable when $\tau = 0$. In order to determine whether or not an increase of the delay away from zero may lead to a loss of stability, we apply Beretta and Kuang criterion, presented in previous sections.

First, we already checked that $a_3(0) + a_6(0) > 0$, in fact one can easily get $a_3(\tau) + a_6(\tau) > 0$ for all τ satisfying (4.3). Hence, **(i)** is satisfied.

Second, it is straightforward that **(ii)** and **(iii)** are satisfied, since

$$-(a_1(\tau)+a_4(\tau))\omega^2+a_3(\tau)+a_6(\tau)+i\left[-\omega^3+(a_2(\tau)+a_5(\tau))\omega\right]\neq 0.$$

Finally, $F(\omega, \tau)$ is given by

$$F(\omega,\tau)=\omega^6+b_1(\tau)\omega^4+b_2(\tau)\omega^2+b_3(\tau),$$

where

$$\begin{aligned}b_1(\tau) &= a_1^2(\tau)-2a_2(\tau)-a_4^2(\tau),\\ b_2(\tau) &= a_2^2(\tau)+2a_4(\tau)a_6(\tau)-2a-1(\tau)a_3(\tau)-a_5^2(\tau),\\ b_3(\tau) &= a_3^2(\tau)-a_6^2(\tau).\end{aligned}$$

Searching for pure imaginary roots of (4.5), $\lambda = i\omega$, as previously detailed one has to determine positive roots of $F(\omega, \tau)$. Since F is a third degree polynomial in ω^2, due to Ruan and Wei [25], one can exhibit conditions on the coefficients $b_i(\tau)$, $i = 1, 2, 3$, for existence of positive roots.

Lemma 4.1 *Let τ satisfy (4.3). Then $F(\cdot, \tau)$ has positive roots if and only if*

$$\begin{aligned}&b_3(\tau)<0 \quad \textit{or}\\ &b_3(\tau)\geq 0,\ b_1^2(\tau)-3b_2(\tau)\geq 0,\ z(\tau)>0 \textit{ and } F(z^2(\tau),\tau)<0,\end{aligned}\tag{4.6}$$

where

$$z(\tau)=\frac{-b_1(\tau)+\sqrt{b_1^2(\tau)-3b_2(\tau)}}{3}.$$

Thanks to condition (4.6), one can define an interval $[0, \tau^*)$ in which it makes sense to search for critical values of the delay τ. For $\tau \in [0, \tau^*)$, let $\omega(\tau)$ be a positive root of $F(\cdot, \tau)$. Then, let $\theta(\tau) \in [0, 2\pi]$ be defined for $\tau \in [0, \tau^*)$ by

$$\begin{aligned}
\cos(\theta(\tau)) &= \frac{(a_5 - a_1 a_4)\,\omega^4 + (a_1 a_6 + a_3 a_4 - a_2 a_5)\,\omega^2 - a_3 a_6}{a_4^2 \omega^4 + \left(a_5^2 - 2 a_4 a_6\right)\omega^2 + a_6^2}, \\
\sin(\theta(\tau)) &= \frac{a_4 \omega^5 + (a_1 a_5 - a_2 a_4 - a_6)\,\omega^3 + (a_2 a_6 - a_3 a_5)\,\omega}{a_4^2 \omega^4 + \left(a_5^2 - 2 a_4 a_6\right)\omega^2 + a_6^2},
\end{aligned}$$

where $\omega = \omega(\tau)$, and we deliberately omit the dependence of the a_i on τ. Since $F(\omega(\tau), \tau) = 0$ for $\tau \in [0, \tau^*)$, it follows that θ is well and uniquely defined for all $\tau \in [0, \tau^*)$. One can check that $i\omega(\tau)$ is a root of (4.5) if and only if τ is a root of the function

$$Z_k(\tau) = \tau - \frac{1}{\omega(\tau)}[\theta(\tau) + 2k\pi], \quad \tau \in [0, \tau^*),\ k \in \mathbb{N}_0.$$

Once again, one can conclude to the stability of the steady state by searching for real roots of a Z_k function.

One may note, however, that finding intervals of values of τ for which the polynomial function F has positive roots ω is getting more and more difficult as the degree of the polynomial part of the characteristic equation increases. Moreover, determining stability of the steady state when the delay τ is zero also necessitates tedious computations in order to apply the Routh-Hurwitz criterion. Consequently, Beretta and Kuang's method to analyze stability of the steady state of a system with delay-dependent coefficients, although very useful for 2 or 3 dimensional systems, rapidly becomes useless from a theoretical point of view (it is always possible to perform numerical simulations in order to locate eigenvalues with positive real parts), unless properties of the steady state itself can lead to simplifications in the characteristic equation (simplifications leading to a decrease in the degree of the polynomial function).

5 Discussion and Remarks

The method presented in the previous section, which allows determining critical values of the delay associated with a loss of stability for the steady state of a system with delay-dependent coefficients, proved to be efficient for 'small' systems, that is with up to 3 variables. For higher order systems,

tedious computations are necessary to determine the characteristic equations, and most of the time it is not possible to achieve interesting results on the stability of the steady state in the absence of delay (Routh-Hurwitz criterion) neither on the location of positive roots of a polynomial function with degree larger than 4.

For systems in low dimensions (up to 3), Beretta and Kuang method is nevertheless very useful and often easy to apply. Hematopoiesis models are in particular adapted to the use of this method, since usually theya re stable in the absence of delay, which allows obtaining relevant results on stability (and the loss of stability) and gaining information on the appearance of oscillations in such systems [2, 8, 14, 15]. It appears that oscillations in blood cell counts may be associated with hematological diseases [12, 13, 18, 23].

Complexity of hematopoiesis leads to consider numerous feedback controls in the regulation of cell population dynamics. Apart from simple models, taking usually into account only one cell population (HSC, erythroid progenitors, etc.), it is often relevant to describe different controls, either short-term or long-term, of one population on an other one. A lot of delays may appear in such modelling, leading to either systems of ordinary differential equations with continuous distributed delay [5, 6] or with several discrete delays [3, 7]. In these cases, the stability analysis is usually much more complicated. There is, to our knowledge, no applicable theory equivalent to the one presented in this manuscript to investigate stability. One exception may be the case of a Gamma distribution for a distributed delay where, using the chain trick, one can reduce the initial system to an ordinary differential equation system [10]. Systems with distributed delays can sometimes reduce to systems with discrete delays, however $\lambda = 0$ may be an eigenvalue in this case (so Beretta and Kuang properties are not always satisfied), see [2, 3, 17].

For systems with continuous distributed delay, a state of the art can be found in Crauste [16]. For systems with several discrete delays, the only option is often to deal with every particular case. Some examples can be found in Adimy et al [3, 7] or Niculescu et al [24], for instance. Biologists continuously asking for more complex models in order to consider the huge amount of information experiments can produce, developing theoretical approaches to deal with stability analysis of less classical delay models can become of strong relevance.

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